Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial

Archives of Cardiovascular Disease (2009) **102**, 485—496

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

CLINICAL RESEARCH

Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial

Impact clinique de l'arrêt définitif du clopidogrel ou du placebo dans l'étude CHARISMA

Jean-Philippe Collet[a], Gilles Montalescot[a,*], Philippe Gabriel Steg[b], Steven R. Steinhubl[c], Keith A.A. Fox[d], Ting Fei Hu[e], S. Claiborne Johnston[f], Christian W. Hamm[g], Deepak L. Bhatt[h], Eric J. Topol[i]

[a] *Inserm unit 937, institut de cardiologie, hôpital Pitié-Salpêtrière, Assistance publique—Hôpitaux de Paris, bureau 236, 47, boulevard de l'Hôpital, 75013 Paris, France*
[b] *Inserm U 698, université Paris-7, Assistance publique—Hôpitaux de Paris, Paris, France*
[c] *Gill Heart Institute, University of Kentucky, Lexington, KY, USA*
[d] *Cardiovascular Research, Division of Medical and Radiological Sciences, University of Edinburgh, Edinburgh, Scotland*
[e] *Cleveland Clinic, Cleveland, OH, USA*
[f] *University of California, San Francisco, CA, USA*
[g] *Kerchoff Heart Center, Bad Nauheim, Germany*
[h] *VA Boston Healthcare System, Brigham and Women's Hospital, Boston, MA, USA*
[i] *The Scripps Research Institute, Scripps Clinic, La Jolla, CA, USA*

Received 25 January 2009; accepted 2 March 2009
Available online 11 June 2009

KEYWORDS
Acute coronary syndrome;
Clopidogrel;
Rebound;
Atherothrombosis

Summary
Background. — Late discontinuation of clopidogrel after an acute coronary syndrome or stent placement may be associated with a clinical rebound effect.
Aims. — To describe the characteristics and evolution of patients non-compliant to study drug in the prospective, randomized, double-blind CHARISMA trial.
Methods. — Of 15,603 patients aged 45 or older years with established atherothrombotic disease (coronary artery disease, stroke, peripheral arterial disease) or multiple cardiovascular

* Corresponding author. Fax: +33 1 42 16 29 31.
E-mail address: gilles.montalescot@psl.aphp.fr (G. Montalescot).

1875-2136/$ — see front matter
doi:10.1016/j.acvd.2009.03.012

risk factors, 2999 permanently interrupted (withdrawers) study drug (clopidogrel or placebo) during follow-up. The primary endpoint was first occurrence since randomization of myocardial infarction, stroke or cardiovascular death.
Results. — Withdrawers displayed a higher risk profile and rates of death/myocardial infarction/stroke (13.5% versus 5.6%; hazard ratio [HR]: 3.18; 95% confidence interval [CI]: 3.05—3.32; $p < 0.001$) and severe bleeding (4.9% versus 0.7%; odds ratio [OR]: 7.42; 95% CI: 5.67—9.70; $p < 0.001$) versus non-withdrawers. Death/myocardial infarction/stroke occurred after an average of 228 days (95% CI: 197—258) and was less frequent in patients assigned to clopidogrel versus placebo (9.7% versus 11.9%; HR: 0.80; 95% CI: 0.64—1.00; $p = 0.051$); the rate of severe bleeding was the same (4.0% versus 4.3%; OR: 0.92; 95% CI: 0.65—1.32; $p = 0.66$). Among withdrawers, initial clopidogrel treatment was an independent correlate of survival (HR: 0.74, 95% CI: 0.59—0.93; $p = 0.011$), but not severe bleeding (OR: 0.94; 95% CI: 0.65—1.35; $p = 0.74$). Kaplan-Meier curves for the primary endpoint suggested no rebound effect or disease reactivation after discontinuation of clopidogrel compared with placebo.
Conclusions. — Patients who stopped medication had increased rates of ischaemic and bleeding events and mortality. Patients initially on clopidogrel had fewer ischaemic events than those on placebo; discontinuation was not associated with any clinically detectable rebound effect.

MOTS CLÉS
Syndrome coronaire aigu ;
Antiagrégant plaquettaire ;
Athérome ;
Infarctus du myocarde ;
Accident vasculaire cérébral ;
Plaquette ;
Interruption

Résumé
Contexte. — L'arrêt du clopidogrel chez des patients stables dans les suites d'un syndrome coronaire aigu ou dans les suites d'une angioplastie avec stent peut être associé à un rebond d'événement cardiovasculaire.
Objectifs. — Décrire les caractéristiques et l'évolution clinique des patients ayant arrêté le traitement à l'étude dans l'essai CHARISMA.
Méthode. — Parmi les 15 603 patients âgés de plus de 45 ans et ayant une maladie athérothrombotique symptomatique (maladie coronaire, accident vasculaire cérébral, artérite des membres inférieurs) ou à haut risque cardiovasculaire, 2999 ont interrompu définitivement le traitement à l'étude (clopidogrel ou placebo) durant le suivi. Le critère primaire de jugement était l'apparition d'un premier événement cardiovasculaire associant infarctus du myocarde ou accident vasculaire cérébral ou décès cardiovasculaire à partir de l'interruption.
Résultats. — Les patients ayant interrompu le traitement à l'étude (clopidogrel ou placebo) avaient un profil de risque plus sévère et ont présenté davantage d'événements cliniques ischémiques définis selon le critère combiné décès/IDM/AVC (13,5 % versus 5,6 % ; HR : 3,18 ; 95 % CI : 3,05—3,32 ; $p < 0,001$) mais également davantage d'hémorragies sévères (4,9 % versus 0,7 % ; OR : 7,42 ; 95 % CI : 5,67—9,70 ; $p < 0,001$) que les patients n'ayant pas interrompu. L'incidence du critère combiné décès/IDM/AVC est survenu dans un délai moyen de 228 jours (95 % CI : 197—258) après l'arrêt et était moins fréquente chez les patients recevant du clopidogrel que chez ceux ayant reçu du placebo (9,7 % versus 11,9 % ; HR : 0,80 ; 95 % CI : 0,64—1,00 ; $p = 0,051$), alors que le taux d'hémorragie sévère était similaire dans les deux groupes (4,0 % versus 4,3 % ; OR : 0,92 ; 95 % CI : 0,65—1,32 ; $p = 0,66$). Parmi les patients ayant arrêté le traitement à l'étude, le traitement initial par clopidogrel avant interruption était un facteur prédictif indépendant de survie (HR : 0,74 ; 95 % CI : 0,59—0,93 ; $p = 0,011$) mais pas de complications hémorragiques majeures (OR : 0,94 ; 95 % CI : 0,65—1,35 ; $p = 0,74$). Les courbes de Kaplan-Meier pour le critère primaire de jugement ne suggèrent pas d'effet rebond ou de réactivation de la maladie après l'arrêt du clopidogrel comparé au placebo.
Conclusion. — Les patients qui ont arrêté le traitement à l'étude dans l'essai CHARISMA sont caractérisés par une augmentation du risque de survenue d'événements ischémiques et hémorragiques majeurs mais aussi de décès. Les patients initialement randomisés dans le groupe clopidogrel ont eu moins de complications ischémiques que ceux sous placebo et l'arrêt du traitement à l'étude n'était pas associé à un effet clinique rebond.

Abbreviations

ACS acute coronary syndrome
CHARISMA clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance
CI confidence interval
DES drug-eluting stents
GUSTO global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries
HR hazard ratio

Background

Discontinuation of antiplatelet therapy in patients with established atherothrombosis has become an increasingly important concern. This is primarily because of the large numbers of patients receiving dual oral antiplatelet therapy after evidence accrued that clopidogrel on top of aspirin provides an additional benefit compared with aspirin alone in ACS and/or after intracoronary stent placement [1—5]. The other reason is that discontinuation of any oral antiplatelet agent appears to be detrimental. Aspirin discontinuation in patients with stable coronary artery disease who are treated with aspirin alone is associated with an increased risk of death [6,7]. The risk of antiplatelet treatment withdrawal is even higher in stented patients, especially when DES have been used [8—13].

Dual oral antiplatelet therapy is now recommended for at least 1 year in patients with a recent ACS or intracoronary DES placement [14]. However, an additional concern is whether discontinuation of clopidogrel late after the acute event in stabilized patients who remain on aspirin is associated with a related hazard. Indeed, premature discontinuation of clopidogrel in patients who underwent intracoronary DES placement is associated with increased mortality in patients despite continuation of aspirin [15]. Whether late discontinuation of clopidogrel, months or years after an ACS or a stent placement or in patients with established atherothrombotic disease, is associated with a clinical rebound effect is unknown.

In the CHARISMA trial, the combination of clopidogrel plus aspirin did not provide a significantly greater protection against cardiovascular events than aspirin alone in a broad population of patients with either cardiovascular risk factors or established atherothrombotic disease, although a significant benefit was observed with dual antiplatelet treatment in patients with established atherothrombotic disease [16]. In the present report, we analysed the baseline characteristics and clinical outcomes of patients randomized in the CHARISMA trial who permanently discontinued the study drug (clopidogrel or placebo) while continuing aspirin therapy. We hypothesized that these patients who interrupt study drug would be at higher risk and may suffer from a rebound effect after clopidogrel cessation.

Methods

Design

The CHARISMA trial was a prospective, multicentre, randomized, double-blind, placebo-controlled study of the efficacy and safety of clopidogrel plus aspirin compared with aspirin alone in patients at high risk for a cardiovascular event [16]. Briefly, patients were eligible for the trial if they were 45 years of age or older and had established atherothrombotic disease (i.e., coronary artery disease, stroke or peripheral arterial disease) or if they had multiple cardiovascular risk factors and had not yet sustained an ischaemic event. Patients were excluded if, in the judgment of the investigator, they had established indications for clopidogrel therapy (such as a recent ACS or stent implantation). Patients scheduled to undergo revascularization were not allowed to enroll until the procedure had been completed.

Definition of discontinuation

Only patients who permanently discontinued the study drug (clopidogrel or placebo) were considered in the present analysis. Reasons for discontinuation included adverse events, moderate or severe bleeding, subject's request, qualifying condition absent or any other reason. Patients who interrupted temporarily (<2 weeks) were not considered in this analysis.

Endpoints

The primary endpoint was the same as that used in the CHARISMA study, that is, first occurrence since randomization of myocardial infarction, stroke (of any cause) or cardiovascular death (including haemorrhage). We also considered cardiovascular death as a coprimary endpoint in the present analysis, given the evidence that withdrawal of an oral antiplatelet agent has been associated with a significant increase in mortality [6,7].

As in the main analysis from the overall trial, the primary safety endpoint was severe bleeding, according to the GUSTO definition, which includes fatal bleeding and intracranial haemorrhage or bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support or surgical intervention.

Statistical analysis

Data were analysed on an intention-to-treat basis, with the inclusion of all patients according to their randomly assigned treatment group and the inclusion of outcomes occurring from randomization to a common study end date (29 August 2005). The time to first occurrence of any event in the composite cluster was used for analysis. Data in patients who did not reach the primary endpoint by the study end date were censored on the date of the patient's last assessment visit. Death from non-cardiovascular causes was treated as a competing event and follow-up was censored on the date of death.

The primary efficacy endpoint of withdrawers compared with non-withdrawers was assessed using a two-sided log-rank test. The treatment discontinuation effect as measured by the HR and its associated 95% CI was estimated using the Cox proportional-hazards model by using time to event from randomization. Cumulative Kaplan-Meier estimates of the event rates from randomization were also calculated to test the clinical outcomes according to study drug discontinua-

Table 1 Baseline characteristics of patients who permanently discontinued the study drug (clopidogrel or placebo) versus non-withdrawers.

	No discontinuation (n = 12,604)	Discontinuation (n = 2999)	p
Demographic			
Age (years)	64 (56—71)	67 (59—74)	<0.001
≥75 years	1872 (14.9)	651 (21.7)	<0.001
Women	3632 (28.8)	1012 (33.7)	<0.001
Body mass index	28.6 ± 5.20	28.7 ± 5.35	0.58
Selected clinical characteristics			
Current smoker	2539 (20.1)	616 (20.5)	0.63
Hypertension	9172 (72.8)	2311 (77.1)	<0.001
Hypercholesterolaemia	9327 (74.0)	2208 (73.6)	0.67
Congestive heart failure	696 (5.5)	230 (7.7)	<0.001
Prior myocardial infarction	4385 (34.8)	1012 (33.7)	0.28
Atrial fibrillation	418 (3.3)	165 (5.5)	<0.001
Diabetes	5271 (41.8)	1285 (42.8)	0.31
Peripheral artery disease	2778 (22.0)	753 (25.1)	<0.001
Prior percutaneous coronary intervention	2868 (22.8)	686 (22.9)	0.89
Prior CABG	2441 (19.4)	638 (21.3)	0.018
Prior stroke	3119 (24.7)	718 (23.9)	0.36
Prior transient ischaemic attack	1431 (11.4)	433 (14.4)	<0.001
Prior carotid endarterectomy	658 (5.2)	167 (5.6)	0.44
Prior peripheral angioplasty or bypass	1356 (10.8)	381 (12.7)	0.002
Diabetic nephropathy	1591 (12.6)	418 (13.9)	0.053

Values are n (%), median (range) or mean ± S.D.; CABG: coronary artery bypass graft.

tion. Cumulative incidence event curves were calculated to investigate the rebound effect or disease reactivation after clopidogrel interruption in comparison to placebo interruption by using time from drug discontinuation to the first primary clinical outcome. Statistical comparisons of the primary safety event rates in the two groups were performed using Pearson's χ^2 test. A multivariable time-dependent Cox model for the overall population was performed to identify independent correlates of mortality. A multivariable logistic model was also performed to assess whether permanent discontinuation was an independent correlate of severe bleeding. All analyses were performed with SAS software (version 8.0, SAS Institute).

Results

Baseline characteristics

Among the 15,603 patients enrolled in the CHARISMA trial, 2999 permanently interrupted the study drug (clopidogrel or placebo) during follow-up. The baseline characteristics of these patients are listed in Table 1. Patients who permanently interrupted the study drug had a higher risk profile compared with those who did not. They were older and were more frequently women. They also presented more vascular comorbidities, along with congestive heart failure and atrial fibrillation (Table 1). The major reason for discontinuation was subjects' request (n = 1299, 43.3%); the other reasons were occurrence of an adverse event (n = 748, 24.9%), severe or moderate bleeding (n = 181, 6.0%), qualifying condition absent (n = 66, 2.2%) and any other reason (n = 705, 23.5%; Table 2). The average delay from randomization to discontinuation was 287 days (95% CI 277—296) and was longer in patients allocated to clopidogrel (306 days; 95% CI 295—318) compared with those allocated to placebo (269 days; 95% CI 259—279; p < 0.001). Time from randomization to discontinuation represented 27.8% of the whole follow-up duration.

Among withdrawers, there was no difference in baseline characteristics between patients who interrupted clopidogrel and those who interrupted placebo (Table 3). Treatment was permanently discontinued by 20.4% of patients in the clopidogrel group compared with 18.2% in the placebo group (p < 0.001) over the whole study period (up to 4 years). A total of 4.8% of the patients in the clopidogrel group and 4.9% of those in the placebo group discontinued treatment because of an adverse event (p = 0.67; Table 2). Discontinuation for moderate or severe bleeding was twice as frequent in the clopidogrel group as in the control group; 99.7% of patients were compliant to aspirin during the entire study follow-up.

Clinical outcomes according to discontinuation versus continuation of study drug

Study-drug withdrawers had worse clinical outcomes than non-withdrawers. The ischaemic endpoints are shown in Table 4. With a median of 28 months of follow-up, the rate of the primary endpoint was increased more than twofold in the withdrawer group (versus non-withdrawers).

Table 2 Reasons for permanent discontinuation of the study drug (clopidogrel or placebo).

	Placebo + aspirin (n = 1415)	Clopidogrel + aspirin (n = 1584)	p
Subject's request	627 (44.3)	672 (42.4)	0.001 (overall χ^2 test)
Adverse event	380 (26.9)	368 (23.2)	
Other reason	319 (22.5)	386 (24.4)	
Qualifying condition absent	33 (2.3)	33 (2.1)	
Moderate or severe bleeding	56 (4.0)	125 (7.9)	

Values are n (%).

Each component of the primary endpoint was increased in withdrawers versus non-withdrawers; in particular, the cardiovascular mortality rate was 5.1% versus 2.5% respectively ($p < 0.001$). These differences were present irrespective of the type of patients (symptomatic versus asymptomatic) and of the reasons for interruption (cessation after an event versus consent withdrawal) (data not shown).

Using a time-dependent multivariable Cox model for the overall population, permanent discontinuation of the study drug was the most powerful independent correlate of cardiovascular mortality (HR: 4.32, 95% CI: 3.66—5.09; $p < 0.001$) along with age, heart failure, previous myocardial infarction, peripheral arterial disease and stroke, whereas concomitant therapy with statin, aspirin and nonsteroidal anti-inflammatory drugs were independently associated with survival (Fig. 1).

Kaplan-Meier curves from randomization to the first event of the primary efficacy endpoint comparing withdrawers with non-withdrawers showed an increase in the incidence of the primary efficacy endpoint ($p < 0.001$) in withdrawers compared with most patients who remained on study drug throughout follow-up (Fig. 2A). The average time from drug discontinuation to primary endpoint was 228 days (95% CI: 197—258), suggesting no immediate causal relationship.

The difference in safety was even more dramatic in patients who interrupted permanently the study drug (Table 4). The rate of the primary safety endpoint (severe bleeding) was 4.9% in the withdrawer group and 0.7% in the non-withdrawer group (OR: 7.42; 95% CI: 5.67—9.70; $p < 0.001$). Of note, the rate of fatal bleeding increased ninefold in withdrawers compared with non-withdrawers. However, when considering patients who stopped the study drug without obvious medical reason or adverse event (i.e., cessation for consent withdrawal or on subject's request), the primary safety endpoint was similar in both groups

Table 3 Baseline characteristics of patients who permanently discontinued the study drug (clopidogrel or placebo).

	Placebo + aspirin (n = 1415)	Clopidogrel + aspirin (n = 1584)	p
Demographic			
Age (years)	66 (59—74)	66 (59—73)	0.76
≥75 years	316 (22.3)	335 (21.1)	0.67
Women	461 (32.6)	551 (34.8)	0.21
Body mass index	28.6 ± 5.34	28.8 ± 5.35	0.27
Selected clinical characteristics			
Current smoker	301 (21.3)	315 (19.9)	0.35
Hypertension	1096 (77.5)	1215 (76.7)	0.63
Hypercholesterolaemia	1055 (74.6)	1153 (72.8)	0.27
Congestive heart failure	102 (7.2)	128 (8.1)	0.37
Prior myocardial infarction	490 (34.6)	522 (33.0)	0.33
Atrial fibrillation	80 (5.7)	85 (5.4)	0.73
Diabetes	585 (41.3)	700 (44.2)	0.12
Peripheral artery disease	365 (25.8)	388 (24.5)	0.41
Prior percutaneous coronary intervention	326 (23.0)	360 (22.7)	0.84
Prior CABG	308 (21.8)	330 (20.8)	0.53
Prior stroke	350 (24.7)	368 (23.2)	0.34
Prior transient ischaemic attack	200 (14.1)	233 (14.7)	0.66
Prior carotid endarterectomy	75 (5.3)	92 (5.8)	0.55
Prior peripheral angioplasty or bypass	189 (13.4)	192 (12.1)	0.31
Diabetic nephropathy	184 (13.0)	234 (14.8)	0.16

Values are n (%), median (range) or mean ± S.D.; CABG: coronary artery bypass graft.

Table 4 Composite and individual primary and secondary endpoints from randomization to end of follow-up in patients who permanently discontinued the study drug.

Endpoint, *n* (%)	No discontinuation (*n* = 12,604)	Discontinuation (*n* = 2999)	Hazard ratio[a] (95% CI)	*p*
Primary efficacy endpoint	702 (5.6)	405 (13.5)	3.18 (3.05—3.32)	<0.001
CV death/MI/stroke	1838 (14.6)	858 (28.6)	2.42 (2.32—2.51)	<0.001
Death	424 (3.4)	321 (10.7)	5.23 (5.08—5.38)	<0.001
Cardiovascular death	313 (2.5)	154 (5.1)	3.53 (3.33—3.73))	<0.001
Non-cardiac death	111 (0.9)	167 (5.6)	9.6 1 (9.36—9.85)	<0.001
Myocardial infarction	241 (1.9)	145 (4.8)	3.04 (2.82—3.27)	<0.001
Stroke	260 (2.1)	181 (6.0)	23.31 (3.10—3.52)	<0.001
Hospitalization	1277 (10.1)	546 (18.2)	1.96 (1.84—2.08)	<0.001
Safety endpoint			Odds ratio (95% CI)	
Any bleed	3167 (25.1)	1276 (42.5)	2.21 (2.03—2.40)	<0.001
Fatal bleed	15 (0.1)	28 (0.9)	7.91 (4.22—14.83)	<0.001
Moderate bleed	114 (0.9)	151 (5.0)	5.81 (4.54—7.43)	<0.001
Severe bleed	87 (0.7)	147 (4.9)	7.42 (5.67—9.70)	<0.001
Symptomatic ICH	24 (0.2)	59 (2.0)	10.52 (6.53—16.94)	<0.001
Minor bleed	3044 (24.2)	1089/2999 (36.3)	1.67 (1.55—1.78)	<0.001

CI: confidence interval; CV: cardiovascular; ICH: intracranial haemorrhage; MI: myocardial infarction.
[a] Hazard ratios calculate by time-dependent Cox model.

(1.5% versus 1.5%). Using a multivariable logistic model, permanent discontinuation of the study drug was found to be an independent correlate of severe bleeding occurring during the whole follow-up (OR: 6.08, 95% CI: 4.62—8.01; $p < 0.001$). Kaplan-Meier curves from randomization to the first event of the primary safety endpoint showed an increase in the incidence of the severe bleeding ($p < 0.001$) in the withdrawers compared to the majority of patients who remained on study drug (Fig. 2B).

Clinical outcomes according to cessation of clopidogrel or placebo

In patients in whom the study drug was withdrawn, the rate of the primary endpoint from randomization remained significantly lower in patients allocated to previous therapy with clopidogrel compared with those allocated to placebo (Table 5). Total mortality was also significantly lower in the clopidogrel group compared with the placebo group, as well as the rate of stroke, while there was no difference in the rate of recurrent myocardial infarction. Results were similar after deletion of events that had occurred before discontinuation and which represented ~20% of the total number of events (Table 5), although the rate of the primary endpoint was no longer significantly lower in patients allocated to previous therapy with clopidogrel compared with those allocated to placebo (Table 5). Using a multivariable Cox model in this population of withdrawers, clopidogrel was independently correlated with survival (HR: 0.74; 95% CI: 0.60—0.95; $p = 0.011$) along with statin therapy, whereas age and prior heart failure were among the most powerful correlates for death (Fig. 3).

Kaplan-Meier curves starting at the time of study drug discontinuation showed an initial sharp decrease in the primary endpoint survival curves in both groups and finally fewer ischaemic events occurred in patients on clopidogrel than in those on placebo (9.7% versus 11.9%; HR: 0.80; 95% CI:

Table 5 Composite and individual primary and secondary endpoints from both randomization and discontinuation to end of follow-up in patients who interrupted placebo versus clopidogrel.

Endpoint	Before and after discontinuation				After discontinuation			
Efficacy endpoint	Placebo (n = 1415)	Clopidogrel (n = 1584)	Hazard ratio (95% CI)	p	Placebo (n = 1415)	Clopidogrel (n = 1584)	Hazard ratio (95% CI)	p
Primary efficacy endpoint	211 (14.9)	194 (12.2)	0.81 (0.67—0.98)	0.034	163 (11.9)	150 (9.7)	0.80 (0.64—1.00)	0.051
CV death/MI/stroke/ hospitalization	447 (31.6)	411 (25.9)	0.79 (0.69—0.90)	<0.001	283 (22.6)	286 (19.6)	0.84 (0.69—0.90)	0.045
Death	173 (12.2)	148 (9.3)	0.76 (0.61—0.94)	0.012	173 (12.2)	148 (9.3)	0.72 (0.58—0.90)	0.004
Cardiovascular death	83 (5.9)	71 (4.5)	0.76 (0.55—1.04)	0.083	83 (5.9)	71 (4.5)	0.72 (0.52—0.99)	0.043
Non-cardiac death	90 (6.4)	77 (4.9)	0.76 (0.56—1.02)	0.071	90 (6.4)	77 (4.9)	0.72 (0.53—0.98)	0.038
Myocardial infarction	69 (4.9)	76 (4.8)	0.98 (0.71—1.36)	0.90	49 (3.5)	59 (3.8)	1.07 (0.73—1.56)	0.73
Stroke	98 (6.9)	83 (5.2)	0.75 (0.56—1.0)	0.048	70 (5.0)	56 (3.6)	0.70 (0.49—1.00)	0.049
Hospitalization	284 (20.1)	262 (16.5)	0.79 (0.67—0.94)	0.007	160 (12.4)	177 (11.8)	0.94 (0.76—1.16)	0.60
Safety endpoints			Odds ratio (95% CI)				Odds ratio (95% CI)	
Any bleed	461 (32.6)	815 (51.5)	2.19 (1.89—2.54)	<0.001	229 (19.4)	290 (27.4)	1.57 (1.29—1.91)	<0.001
Fatal bleed	13 (0.9)	15 (0.9)	1.03 (0.49—2.17)	0.94	13 (0.9)	15 (0.9)	1.03 (0.49—2.17)	0.94
Severe bleed	69 (4.9)	78 (4.9)	1.01 (0.72—1.41)	0.95	61 (4.3)	63 (4.0)	0.92 (0.65—1.32)	0.70
Moderate bleed	54 (3.8)	97 (6.1)	1.64 (1.17—2.31)	0.004	46 (3.3)	75 (4.8)	1.49 (1.03—2.17)	0.035
Symptomatic ICH	29 (2.0)	30 (1.9)	0.92 (0.55—1.55)	0.76	25 (1.8)	25 (1.6)	0.89 (0.51—1.56)	0.69

CI: confidence interval; CV: cardiovascular; ICH: intracranial haemorrhage; MI: myocardial infarction.

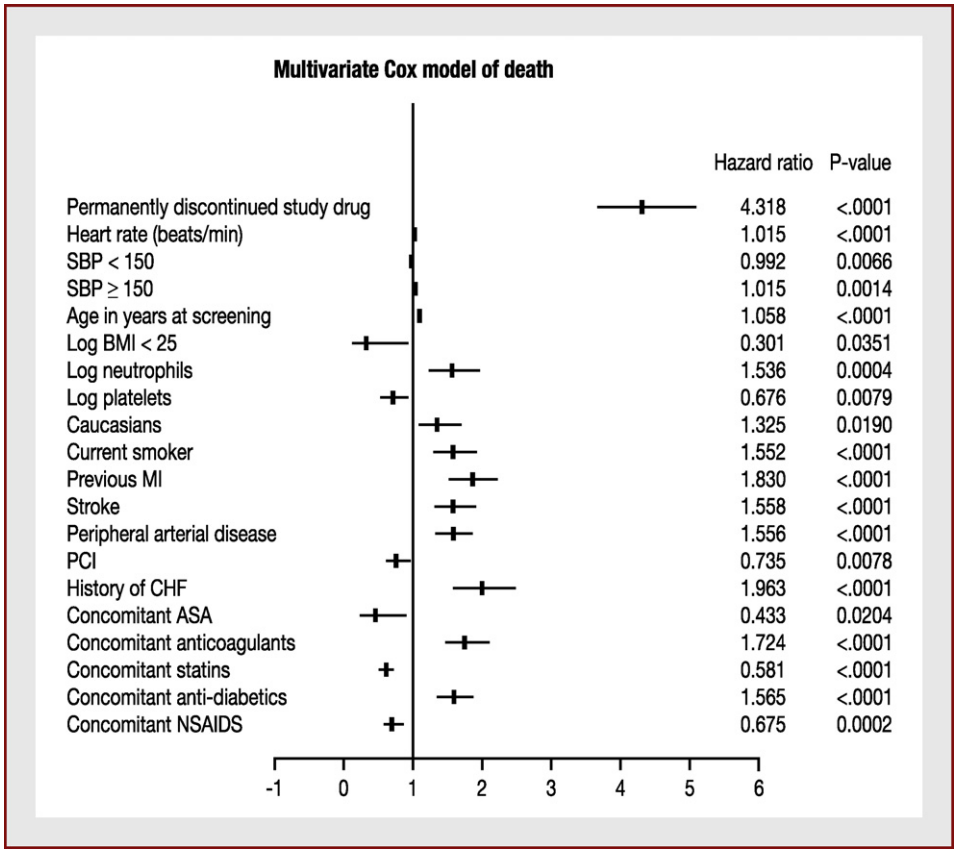

Figure 1. Independent correlates of cardiovascular death in the global population.

0.64—1.00; $p = 0.051$), with no suggestion of rebound or disease reactivation after clopidogrel interruption compared to placebo discontinuation (Fig. 4A). Similar Kaplan-Meier curves were found for mortality (data not shown).

Regarding severe bleeding, there was a sharp initial decrease in survival curves of both groups and finally there was no difference in severe bleeding rates between patients discontinuing clopidogrel or placebo (Table 5 and Fig. 4B). Most of the significant bleeding events, including moderate and severe bleeds, occurred after discontinuation of the study drug. Kaplan-Meier curves from the time of study-drug discontinuation to the first event of the primary safety endpoint showed no difference between patients receiving clopidogrel compared with those on placebo (4.0% versus 4.3%; OR: 0.92; 95% CI: 0.65—1.32; $p = 0.67$) (Fig. 4B). Time delays of severe bleeding according to randomization or drug discontinuation were similar when considering discontinuation of clopidogrel or placebo. In multivariable analysis, clopidogrel discontinuation was not independently correlated to severe bleeding (OR: 0.94; 95% CI: 0.65—1.35; $p = 0.74$).

Discussion

The present work shows that permanent discontinuation of the study drug (clopidogrel or placebo) occurs in a substantial proportion (19.3%) of the study population, which is consistent with previous reports on drug interruption in clinical trials and with data on compliance to treatment [17—19]. An important finding is that discontinuation of study drug identifies a very high-risk group of patients exposed to more frequent ischaemic events, increased mortality and also more frequent severe bleeding when considering events occurring during the whole follow-up. In the subgroup that discontinued the study drug and after deleting events that occurred before discontinuation, initial allocation to clopidogrel was associated with a trend for fewer ischaemic events and was independently correlated with survival, without the suggestion of any clinical rebound in this population with stabilized atherothrombosis.

Thienopyridine therapy in combination with low-dose aspirin has become the mainstay antiplatelet treatment in ACS for up to 1 year irrespective of clinical presentation or coronary revascularization procedures [2—4,14]. Consistent analyses have shown that the benefits emerge rapidly after the first oral administration of clopidogrel [1,3,4] and data beyond 30 days suggest further incremental benefits [20]. Whether the absolute difference continues to widen significantly beyond 3 months is still debated, but there may be a potential hazard of premature clopidogrel discontinuation within the first year of follow-up [10,21,22].

The hazard related to discontinuation of antiplatelet agents depends upon many factors. The most critical factor is stent implantation [23], with mortality rates ranging from 5 to 15% when interruption of both agents occurs early after implantation [9,24]. Discontinuation of clopidogrel within the first month following implantation of

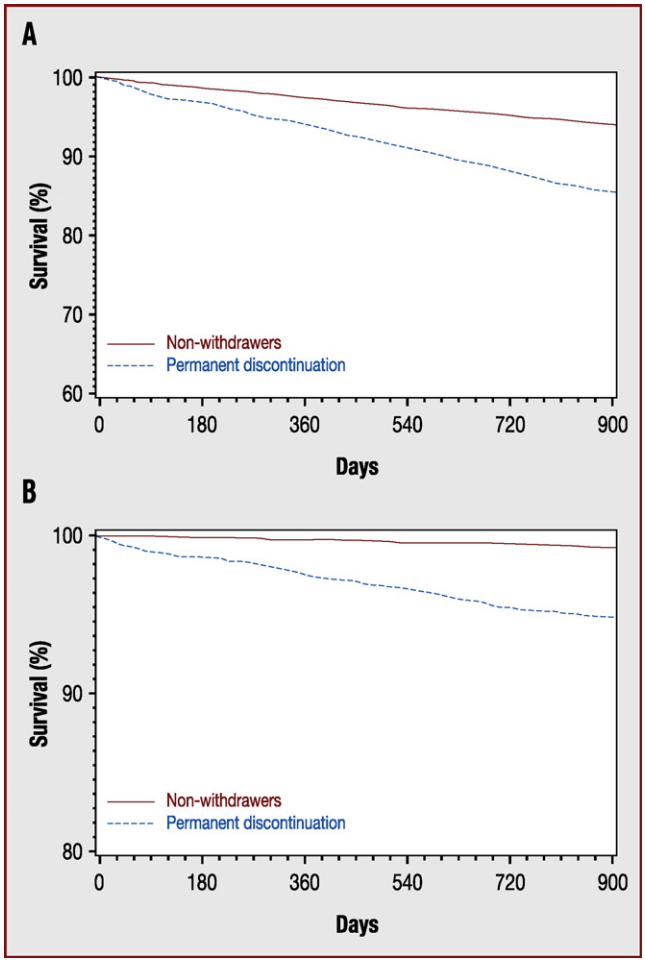

Figure 2. Kaplan-Meier survival curves from randomization to first event for (A) the primary efficacy endpoint and (B) the primary safety endpoint, comparing patients who discontinued the study drug with non-withdrawers (log-rank test, $p < 0.001$ for both efficacy and safety endpoints). Events that occurred before and after discontinuation have been considered.

a DES is associated with a marked increase of early stent thrombosis and cardiovascular death [15]. Late interruption of clopidogrel also remains a concern with DES, although conflicting information has been published [8,10,25—27]. Extending beyond ACS and DES, the randomized CHARISMA study provides a unique opportunity to assess the impact of clopidogrel discontinuation in stable atherothrombotic patients, whether symptomatic or not.

Patients with a recent ACS or a DES implantation or any other condition in which clopidogrel treatment was required were not enrolled in CHARISMA. The present analysis shows that patients interrupting therapy (clopidogrel or placebo) are at particular high risk of further ischaemic events and death [7,19]. All kinds of events were increased among withdrawers (versus non-withdrawers). The excess of risk in withdrawers may be explained by more serious demographic characteristics and they were also more likely to have preexisting established atherothrombotic disease. In addition, a substantial proportion of withdrawers experienced an adverse event during follow-up, which may have sometimes, rightly or not, motivated discontinuation. All of these characteristics in withdrawers depict a subgroup at particular high risk, in addition to the possibility of more frequent poor compliance to other treatments in this group. Consent withdrawal was the principal reason for study drug interruption and this may be seen as an indicator of poor compliance.

Previous randomized double-blind trials have shown that drug discontinuation is associated with worse outcomes irrespective of assignment to active drug or placebo [18]. In the present analysis, patients on clopidogrel had slightly better outcomes than patients on placebo after discontinuation, although there was no effect on the occurrence of myocardial infarction. Some ''carryover'' effect and the high risk profile of withdrawers may account in part for this finding, so that patients keep having a benefit from prior exposure to an active drug treatment even with a limited, although sufficiently long, period of exposure (286 days on average). In a similar manner to the results in the subgroup of non-withdrawers, other high-risk subsets of the CHARISMA study population drew a significant benefit from dual antiplatelet therapy (e.g., symptomatic patients, CAPRIE-like patients [28]), whereas this treatment strategy was not effective in the main analysis [29]. Our results also indicate that there was no detectable clinical rebound or reactivation of atherothrombotic disease after withdrawal. Kaplan-Meier curves (clopidogrel versus placebo) from the time of study drug discontinuation to the first event tended to be parallel over time, suggesting a sustained benefit of clopidogrel after discontinuation without any rebound effect. It is likely that chronic aspirin treatment in these stable patients may have offered sufficient protection after clopidogrel withdrawal in the majority of cases. This is a major distinction from patients presenting with ACS and/or undergoing DES placement, who may have persistent platelet activation, uncontrolled by aspirin, with a rebound of thrombotic events after clopidogrel discontinuation, as is now reported in several studies [10,22].

Finally, this study shows an impressive relation between discontinuation and mortality, which doubled in withdrawers compared with non-withdrawers. The fact that discontinuation was an independent predictor of death further highlights the high risk of withdrawers. Similar conclusions were found for severe bleeding, which was dramatically more frequent in withdrawers versus non-withdrawers. This is accounted for by the fact that withdrawers have factors common to ischaemic risk and bleeding risk, such as age, sex, renal failure and heart failure, and they may also have had a more frequent history of minor or serious bleeding, an indicator of bleeding risk.

The limitations of the present study are inherent to any subgroup analysis including patient selection bias and use of non-randomized groups. The potential differences in time of follow-up for events occurring after discontinuation and the impact of possible open-label clopidogrel intake after interruption represent potential biases. Although the majority of events defined as the primary ischaemic and safety endpoints of the study occurred after discontinuation in the group of withdrawers, these events may have been the same as the one motivating interruption of study drug. We also lack information on patients who may have interrupted other therapies or on patients who may have undergone bare-metal or DES implantation during the period of follow-up. The increased risk of severe

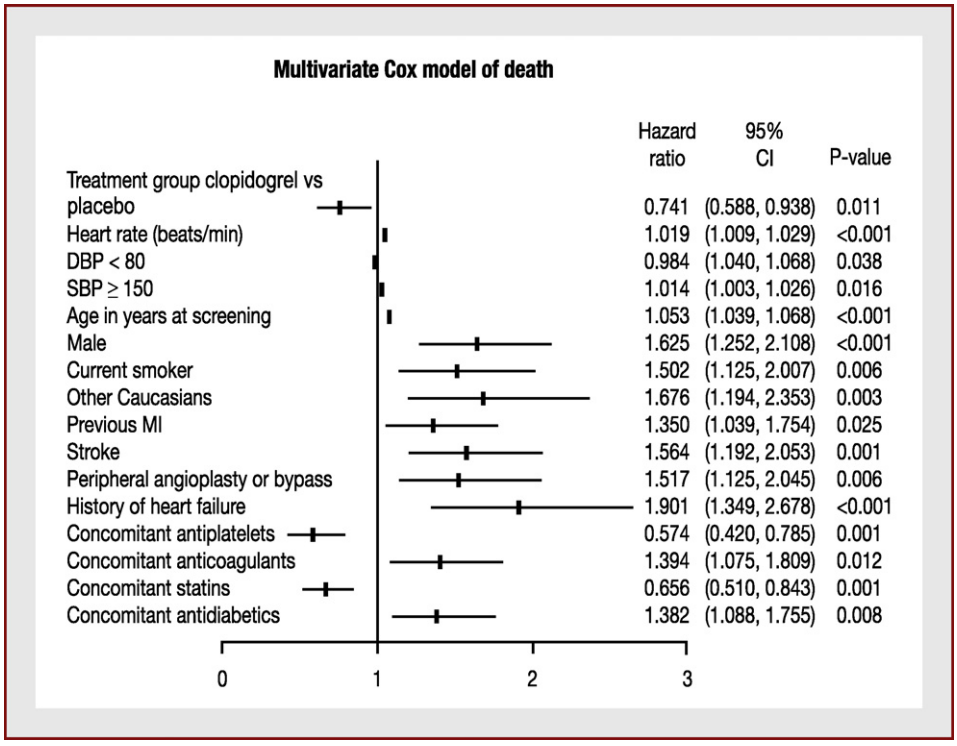

Figure 3. Independent correlates of cardiovascular death in the population who discontinued the study drug ($n = 2999$).

bleeding with discontinuation is puzzling and in addition to the hypotheses discussed above, deficiencies in diagnostic coding may obscure the reasons why study drug was stopped in the trial. The time analyses of bleeding events from randomization but also from discontinuation do not indicate any significant decrease in severe bleeding after clopidogrel interruption whereas there was a clear excess of bleeding early after clopidogrel exposition in the overall population of the CHARISMA trial [29]. It is possible that withdrawers have a different risk profile for bleeding, more frequently a prior history of bleeding before randomization, which led them eventually to stop the study drug. More than 50% of severe bleeding events occurred on aspirin alone, after the study drug discontinuation, and in particular after clopidogrel interruption, further emphasizing that individual susceptibility to severe bleeding was present before randomization and is inherent to patients' characteristics rather than to exposure to the study-drug. The difference in time delay from randomization to interruption between patients assigned to clopidogrel versus placebo (268 versus 306) further supports this assumption and might be explained by the early excess of moderate or severe bleeding in patients exposed to clopidogrel, as shown previously [29]. Obviously, our withdrawer population is highly specific and would not have been suitable for a randomized trial evaluating interruption strategies of clopidogrel therapy.

In conclusion, patients who permanently discontinued the study drug (clopidogrel or placebo) in the CHARISMA trial represent a significant proportion of the overall population with high-risk features and increased rates of ischaemic and bleeding events, as well as mortality. Patients initially assigned to clopidogrel had fewer ischaemic events compared with those assigned to placebo and discontinuation was not associated with any clinically detectable rebound effect. Assessment of the risk of discontinuation warrants further investigation in appropriately designed studies comparing maintenance to or discontinuation of clopidogrel in high-risk atherothrombotic patients.

Disclosures

Dr Montalescot discloses the following relationships: Research Grants from Bristol-Myers Squibb, Sanofi-Aventis Group, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération française de cardiologie; Consulting fees from Sanofi-Aventis Group, Eli Lilly, Bristol-Myers.

Squibb, Merck Sharpe and Dohme, GlaxoSmithKline, The Medicines Company, and Schering-Plough. He has also received lecture fees from Sanofi-Aventis, Eli Lilly, Bristol-Myers Squibb, Merck Sharpe and Dohme, Cordis, GlaxoSmithKline, and Schering-Plough.

Dr Bhatt discloses the following relationships: Honoraria (donated to non-profits for more than 2 years) — Astra Zeneca, Bristol-Myers Squibb, Centocor, Daiichi-Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Millennium, Paringenix, PDL, sanofi-aventis, Schering Plough, The Medicines Company, TNS Healthcare; Speaker's bureau (more than 2 years ago) — Bristol-Myers Squibb, sanofi-aventis, The Medicines Company; Consultant/Advisory Board (any honoraria donated to non-profits) — Astra Zeneca, Bristol-Myers Squibb, Cardax, Centocor, Cogentus, Daiichi-Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Johnson and Johnson, McNeil, Medtronic, Millennium, Otsuka, Paringenix, PDL, Philips,

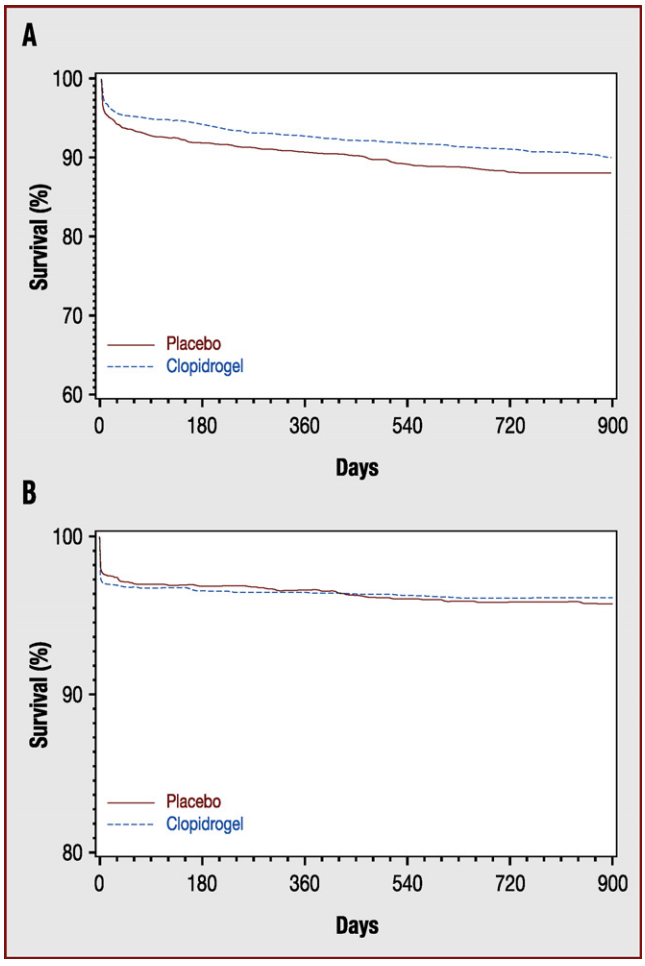

Figure 4. Kaplan-Meier survival curves from time of study drug discontinuation to first event for (A) the primary efficacy endpoint and (B) the primary safety endpoint, comparing patients who discontinued clopidogrel with those who discontinued placebo (log-rank test, $p = 0.051$ for efficacy endpoint 0.95 for safety endpoint). Only events that occurred after discontinuation have been considered.

Portola, sanofi-aventis, Schering Plough, The Medicines Company, tns Healthcare, Vertex; Expert testimony regarding clopidogrel (the compensation was donated to a non-profit organization).

Dr Steg discloses the following relationships: honoraria for advisory board attendance and consulting fees from Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharpe and Dohme, Nycomed, sanofi-aventis, Servier, Takeda, The Medicines Company; speakers bureau from Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Nycomed, sanofi-aventis, Servier, ZLB Behring and a research grant from sanofi-aventis within the past 3 years.

Dr Topol discloses the following relationship: Research Grants — Sanofi-Aventis, Bristol-Myers Squib.

Dr Steinhubl discloses the following — salary/employment — The Medicines Company. Research support from The Medicines Company and Eli Lilly/Daiichi Sankyo. Honoraria as a consultant for The Medicines Company, Eli Lilly/Daiichi Sankyo, Bristol-Myers Squibb, Sanofi Aventis, Astra Zeneca, Portola, Arena Pharmaceuticals, Scios, and Cardax.

Dr Collet discloses the following: Research grants from Bristol-Myers Squibb, Sanofi-Aventis Group, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération française de cardiologie; Consulting fees from Sanofi-Aventis Group, Eli Lilly, Bristol-Myers Squibb. He has also received lecture fees from Sanofi-Aventis, Eli Lilly, Bristol-Myers Squibb, Merck Sharpe and Dohme, Cordis, GlaxoSmithKline.

References

[1] Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607—21.
[2] Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The task force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J 2005;26:804—47.
[3] Steinhubl SR, Berger PB, Mann 3rd JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411—20.
[4] Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494—502.
[5] Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation 2002;105:1760—3.
[6] Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J 2006;27:2667—74.
[7] Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110:2361—7.
[8] Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2006 [published online: Dec 5, 2006: doi:10.1001/jama.297.2.joc60179].
[9] Kaluza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288—94.
[10] Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006;48:2584—91.
[11] Vicenzi MN, Meislitzer T, Heitzinger B, et al. Coronary artery stenting and non-cardiac surgery — a prospective outcome study. Br J Anaesth 2006;96:686—93.
[12] Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056—61.
[13] Roiron C, Sanchez P, Bouzamondo A, et al. Drug eluting stents: an updated meta-analysis of randomised controlled trials. Heart 2006;92:641—9.
[14] Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363—72.
[15] Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopy-

ridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803—9.
[16] Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706—17.
[17] Allen LaPointe NM, Kramer JM, DeLong ER, et al. Patient-reported frequency of taking aspirin in a population with coronary artery disease. Am J Cardiol 2002;89:1042—6.
[18] Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet 2005;366:2005—11.
[19] Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med 2006;166:1842—7.
[20] Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. Circulation 2003;107:966—72.
[21] Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA 2008;299:532—9.
[22] Malinin A, Pokov A, Spergling M, et al. Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12(R) rapid analyzer: the verify thrombosis risk assessment (VERITAS) study. Thromb Res 2007;119:277—84.
[23] Collet JP, Montalescot G. Premature withdrawal and alternative therapies to dual oral antiplatelet therapy. Eur Heart J 2006;8(Suppl. G):G46—52.
[24] Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol 2007;49:122—4.
[25] Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030—9.
[26] Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020—9.
[27] Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989—97.
[28] CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329—39.
[29] Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007;49:1982—8.